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Evaluation of Neutropenia and Neutrophilia in Preterm Infants

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Abstract

Neutropenia and neutrophilia are encountered frequently in neonatal intensive care units worldwide. In this article, we review normal blood neutrophil concentrations in preterm infants and provide an outline for the clinical and laboratory evaluation of neutropenia and neutrophilia in the neonatal period.

Keywords

neonate; neutropenia; neutrophilia; reference ranges; leukemoid

Neutrophil counts are used routinely as part of the sepsis evaluation in neonatal intensive care units (NICUs) worldwide, and both neutropenia and neutrophilia are documented frequently in newborn infants. In this article, we review the normal blood neutrophil concentrations and the definitions of neutropenia and neutrophilia, and provide an outline for clinical and laboratory evaluation of these disorders in the neonatal period.

Normal blood neutrophil concentrations in neonates

The absolute neutrophil count (ANC) can be calculated from a routine complete blood count (CBC) by multiplying the white cell count (/μL) with the sum of segmented and band neutrophil percentages on the differential count. The ANC value can then be interpreted by comparison with one of several available reference ranges (1–3). Manroe *et al.*(4) were the first to compile references ranges for blood neutrophil concentrations in neonates, using data from a cohort of 434 neonates born at 38.9 ± 2.4 weeks gestation. They showed that the neutrophil counts peaked at 12–24 hours with 95% confidence limits of 7,800–14,500/μL

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and then stabilized at a lower value of 1,750 by 72 hours of life. A stable upper limit was achieved at 6.6 days of age.

The reference ranges reported by Manroe *et al.* were useful for term and late preterm neonates but did not include many preterm infants (5–8). To address this deficiency, Mouzinho *et al.*(3) compiled ANC values from 1,788 CBCs drawn from 63 neonates born at 29.9 ± 2.3 weeks gestation. Their revised charts were comparable to those from Manroe *et al.* near the upper limits of blood neutrophil concentrations but showed greater variation at the lower limit.

In a recent study, Schmutz *et al*. (1) compiled a new set of reference ranges for blood neutrophil concentrations using data from 30,354 CBCs from neonates born at 23–42 weeks' gestation. Besides the large sample size, a major strength of this study was the use of automated blood counting instrumentation, which allows the enumeration of a larger and consistent number of cells for each report and eliminates inter-observer variability in visual identification of neutrophils (9). In the interval between 72 and 240 hours after birth, the ANC ranged between 2700–13,000/μL (5^{th}–95^{th} percentile) for infants >36 weeks gestation, between 1000–12,500/μL at 28–36 weeks, and 1300–15,300/μL at <28 weeks gestation. The upper limits of ANC in this data set were significantly higher than ranges reported by both Manroe and Mouzinho, which was unexpected but could be due to the methodological differences or might be a biological effect of high altitude at which the participating centers were located (10, 11).

Neutropenia

In a statistical sense, neutropenia is defined as an ANC less than 2 standard deviations below the mean value for age (12) or alternatively, below the 5^{th} percentile for an age-defined population (2, 3). Mouzinho *et al.* defined neutropenia as an ANC<1100/μL, which was a more stringent definition than the 1800/μL limit proposed by Manroe *et al.*(2, 3). In infants admitted to NICUs, neutropenia can be seen in up to 6–8% of all patients (1, 13–16). The incidence of neutropenia increases with decreasing birth weight, seen in 3% term infants weighing >2500g, 13% infants weighing <2500 g, and up to 38% of those weighing less than 1000 grams (13, 17).

In neonates who are neutropenic but otherwise asymptomatic, the relationship between low ANC and risk of infection remains speculative and is an extrapolation from children with neutropenia related to Kostmann's syndrome or due to chemotherapy. Whereas neonates with an ANC >1,000/μL are unlikely to be at significantly increased risk of secondary infections, an ANC<500/μL may be more likely to increase the risk, particularly if neutropenia persists for more than a few days (18–20). An ANC between 500–1,000/μL may indicate some intermediate risk (21). Besides the severity of neutropenia, the risk of infection in a neutropenic neonate is also affected by the overall severity of illness and the presence of co-morbidities, which may increase the need for invasive monitoring. In very low birth weight infants, the risk of infection secondary to neutropenia and the mortality attributable to infection in the setting of neutropenia are significantly higher than in term newborns (22). Finally, the duration of neutropenia is an important consideration and infants with mild-moderate neutropenia for >7–10 days should be evaluated further (21).

Clinical evaluation of neutropenia in neonates

Neutropenia can be secondary to decreased production of neutrophils, increased neutrophil destruction, or a combination of these mechanisms (Table 1). Neonatal neutropenia occurs most frequently in association with maternal hypertension, sepsis, twin-twin transfusion, alloimmunization, and hemolytic disease (21).

In many infants, maternal history of hypertension or pre-eclampsia with fetal growth retardation, multiple gestation with disparity between twins, or an infectious illness during pregnancy can be diagnostic. Similarly, a history of prolonged rupture of membranes or chorioamnionitis can indicate increased risk of early-onset sepsis. Sepsis-induced neutropenia is usually transient and resolves with recovery from sepsis, but in a critically-ill infant with multi-system dysfunction, neutropenia could be a sign of overwhelming sepsis and bone marrow depression (22). Less frequently, neutropenia could occur in association with other life-threatening, but clinically-obvious, conditions such as necrotizing enterocolitis, cardiomyopathy (Barth syndrome), and inborn errors of metabolism (intractable metabolic acidosis or other electrolyte derangements).

In a well-appearing infant with persistent neutropenia, an immune-mediated etiology involving anti-neutrophil antibodies should be considered (23–27), such as alloimmune neonatal neutropenia, neonatal autoimmune neutropenia, and autoimmune neutropenia of infancy (28). Alloimmune neonatal neutropenia occurs due to maternal sensitization to a paternal antigen present on the neutrophils of her fetus, and produces specific antibodies that are transported across the placenta and cause neutropenia in fetus (24). Neonatal autoimmune neutropenia results from the transmission of pre-existing maternal anti-neutrophil autoantibodies, often due to an autoimmune disease such as lupus in the mother, into the fetus (24, 25). Unlike these two disorders caused by maternal antibodies, autoimmune neutropenia of infancy is a transient autoimmune phenomenon where the infant’s own immune system produces the anti-neutrophil antibodies (27).

In a neutropenic infant, physical examination may show signs of sepsis, intra-uterine growth retardation, or pallor or petechiae (indicating concomitant depression of another hematological lineages). Less frequently, dysmorphic features such as skeletal dysplasia, radial or thumb hypoplasia (congenital bone marrow failure syndromes), hepatosplenomegaly (TORCH infections, storage disorders), or skin/hair pigmentary abnormalities (Chédiak-Higashi syndrome) can be helpful.

The chronological age of the infant can provide useful clues towards the etiology of neutropenia (21). Neutropenia associated with maternal hypertension is usually observed in the 1st postnatal week and persistence >10 days should indicate a need for further evaluation. Congenital bone marrow failure syndromes also can present early. Inborn errors of metabolism usually present late in the 1st week and beyond. Copper deficiency is a consideration in infants with short bowel syndrome who are dependent on parenteral nutrition. Idiopathic neutropenia of prematurity occurs in convalescing very low birth infants and resolves spontaneously.

Laboratory evaluation of neutropenia in neonates

The CBC should be evaluated to determine whether neutropenia is isolated or is associated with anemia and/or thrombocytopenia, which may indicate the presence of a generalized bone marrow failure syndrome. The differential leukocyte counts can also be used for kinetic evaluation of the neutrophil lineage by calculating the 'immature to total neutrophil (I:T) ratio' [=(bands + metamyelocytes + myelocytes)/(segmented neutrophils + bands + metamyelocytes + myelocytes)]. An elevated I:T ratio (≥ 0.3) in the presence of neutropenia reflects depletion of the neutrophil storage pool in the bone marrow due to increased peripheral destruction or recruitment of neutrophils into inflamed tissues, and in most instances, increased neutrophil production. In contrast, a normal/low I:T ratio in a neutropenic infant may indicate decreased neutrophil production. The I:T ratio retains its discriminatory value for sepsis in premature infants and can be employed in conjunction with other screening tests such as C-reactive protein concentrations (29–31).

A bone marrow biopsy should be considered in infants with prolonged (>2 wks), unusual, or severe neutropenia refractory to treatment with recombinant granulocyte-colony stimulating factor. The procedure is usually performed in the tibial marrow using an Osgood needle and has been described elsewhere (32). Bone marrow evaluation can provide useful kinetic information, including the size of the proliferative and the post-mitotic storage pools of neutrophils. Reduction in both cellular populations suggests decreased marrow production, while increased numbers of proliferative precursors with a depleted storage pool is consistent with increased peripheral destruction of neutrophils. A combination of an expanded proliferative pool with a normal storage pool is generally seen during marrow recovery, and is relatively non-specific (33, 34).

Clinical management of neutropenia in neonates

The clinical approach to a neutropenic neonate should depend on the severity, duration, and etiology of the disorder. In a critically-ill infant, sepsis should be a part of the differential diagnosis and antibiotic therapy should be started pending culture maturation. If the neutropenia is severe and prolonged, reverse isolation procedures may be considered. We also consider treatment with recombinant granulocyte-colony stimulating factor (G-CSF) until the ANC recovers to normal. Details of clinical management of neutropenia are beyond the scope of this article and are available elsewhere (35).

Neutrophilia

Neutrophilia can be defined as an ANC greater than 2 standard deviations above the mean value for age, or alternatively, above the 95th percentile for an age-defined population (1, 11). When defined as 2 standard deviations above mean, 2.5 percent of normal neonates will have an ANC above this value. There is no single accepted definition for neutrophilia, which is a reflection of the variability in neutrophil counts in the first 72 hours of life. The 95th percentile for ANC at 72 hours of age corresponds to 7000/μL in the Manroe charts (4). Mouzinho *et al.* (3) defined neutrophilia as >15,000/mm^3 in the first 60 hours of life, and >6000/mm^3 thereafter. In the reference ranges proposed recently by Schmutz *et al.* (1), neutrophilia would be defined as >13,000/μL. The term 'leukemoid reaction' has been used

when the ANC value is more than 10 standard deviations above the mean for age, or shows more than 5% blast forms, promyelocytes, or myelocytes on the differential blood cell count (11).

Juul *et al.* (36) reviewed a total of 2038 CBCs from 347 preterm infants admitted to their NICU and recorded neutrophilia in 146 infants (42% incidence). They noted that the magnitude and duration of neutrophilia was greater at earlier gestational ages, possibly due to immaturity of granulopoietic function. When all infants are considered (with and without infection), 95% of infants 24 to 26 weeks, 54% of infants 27 to 29 weeks, 27% of infants 30 to 34 weeks, and 29% of infants >35 weeks had at least one neutrophilic event. Neutrophilia in stable infants ≥27 weeks' gestation generally occurred during the first 3 weeks of life (except when associated with sepsis). In contrast, in the smallest infants, neutrophilia often persisted for up to 4 months.

Clinical evaluation of neutrophilia in neonates

In infants with neutrophilia, transient elevations in blood neutrophil concentrations may be due to one or more of four possible kinetic mechanisms: (1) accelerated neutrophil production; (2) accelerated release of neutrophils from the bone marrow into the blood; (3) neutrophil demargination; or (4) diminished egress of neutrophils from the blood into the tissues (11). Causes of neutrophilia are summarized in Table 2.

In newborn infants, high neutrophil counts are common on the 1st day following delivery and therefore, have low specificity as a sign of sepsis or another pathological condition (1). Infants delivered vaginally normally have higher neutrophil counts than those delivered by cesarean section with no preceding labor, indicating that this transient rise in neutrophil counts may be caused by, at least in part, by the stress of labor/delivery and associated rise in catecholamine concentrations, which can promote demargination of neutrophils in the microvasculature. Because these physiological 1st day elevations in neutrophil count are not associated with a "left shift", the peak is probably not the kinetic result of accelerated production and release of neutrophils from the marrow into the blood (1). During the first 18 hours following delivery, neonates delivered by cesarean section following labor had an average neutrophil concentration of 12,020/μL, compared with 8,650/μL for those born by cesarean section with no preceding labor.

The most frequent causes of neutrophilia in neonates include infection, antenatal or postnatal treatment with corticosteroids, occasionally, a chromosomal defect such as Down's syndrome. Corticosteroids cause neutrophilia due to release of neutrophils from the marrow and also because of a transient suppression of adhesion molecule expression and reduce egress from the circulation (36). Occasionally, an adhesion molecule deficiency can present with marked elevation in neutrophil counts, delayed separation of umbilical cord, and/or serious systemic infections (21).

Laboratory evaluation of neutrophilia in neonates

In infants with an elevated ANC, the I:T ratio can provide useful kinetic information. Most infants with a high ANC but a normal/low I:T ratio have a benign, transient elevation in

neutrophil concentrations, most likely related to accelerated release from the mature storage pool in the bone marrow, decreased egress into tissues, or demargination.

Infants with extreme elevations in total white cell counts and ANC ('leukemoid' reaction) should be evaluated for sepsis, TORCH infections, and chromosomal anomalies such as Down's syndrome. Patients with Down's syndrome may show a "left shift" on a CBC and an enlarged neutrophil proliferative pool in the marrow, indicating a transient rise in neutrophil production due to increased G-CSF production (11, 29). Transient leukocytosis has been observed in infants with CD11/CD18 deficiency, and this diagnosis might account for an occasional case of transient neonatal leukemoid reaction (30).

Clinical management of neutrophilia in neonates

Management is focused on the primary disease. Complications such as hyperviscosity or electrolyte abnormalities are rare, even in infants with extreme elevations in white cell counts (11).

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Table 1

Causes of Neutropenia in Neonates

Decreased neutrophil production
Infants of hypertensive mothers (unknown; possible causes include presence of a placenta-derived inhibitor of neutrophil production)
Donors of twin-twin transfusions
Neonates with Rh hemolytic disease (precursors diverted towards erythroid differentiation to increase RBC production)
Congenital Neutropenias
Bone Marrow Failure Syndromes
Kostmann syndrome (maturation arrest and increased apoptosis of precursors; neutrophil elastase mutations)
Reticular dysgenesis (severe combined immunodeficiency with impairment of both myeloid and lymphoid production)
Barth syndrome (organic aciduria, dilated cardiomyopathy, and neutropenia)
Shwachman-Diamond syndrome (exocrine pancreatic insufficiency, failure to thrive, skeletal abnormalities, and neutropenia; defect in SBDS protein, which may be involved in ribosomal biogenesis)
Cartilage-hair hypoplasia (short-limbed dwarfism; impairment of proliferation in neutrophil precursors)
Cyclic Neutropenia (cyclic hematopoiesis with nadirs at 3-week intervals; associated with neutrophil elastase mutations that prevent membrane localization of the enzyme)
Inborn Errors of Metabolism
Organic acidemias (loss of neutrophil precursors)
Glycogen storage disease type 1b (increased neutrophil apoptosis)
Viral infections (infection of neutrophil progenitors, hypersplenism)
Cytomegalovirus
Rubella
Copper deficiency
Alloimmune neutropenia associated with anti-HNA-1b antibodies (antigen present on neutrophil precursors)
Increased neutrophil destruction
Bacterial or fungal sepsis (increased tissue migration; marrow suppression in severe cases)
Necrotizing enterocolitis (egress into intestines and peritoneum)
Anti-neutrophil antibody-mediated disorders (alloimmune neonatal neutropenia, neonatal autoimmune neutropenia, and autoimmune neutropenia of infancy
Idiopathic neutropenia of prematurity (precursors diverted towards erythroid differentiation to compensate for anemia of prematurity)
Drug-induced neutropenia (β-lactam antibiotics, thiazides, ranitidine, acyclovir)
Pseudoneutropenia (benign condition; circulating neutrophil pool is smaller than the vascular marginated pool)
Artifactual Neutropenia (benign condition; neutrophils agglutinate upon exposure to ethylenediaminetetraacetic acid, an anticoagulant used in blood collection tubes)

Table 2

Causes of Neutrophilia in Neonates

Accelerated neutrophil production
Sepsis
TORCH infections
Down's syndrome, Trisomy 21 mosaicism
Treatment with recombinant granulocyte-colony stimulating factor, recombinant granulocyte macrophage-colony stimulating factor
Hereditary neutrophilia (autosomal dominant, hepatosplenomegaly, increased alkaline phosphatase, Gaucher type histiocytes in marrow)
Associated with amegakaryocytic thrombocytopenia and with congenital deformities such as tetralogy of Fallot, dextrocardia and absent radii
Chronic marrow stimulation as in hemolytic anemia, thrombocytopenia
Accelerated release of neutrophils from the bone marrow into the blood
Corticosteroid administration
Epinephrine administration
Sepsis
Stress of delivery/labor; neutrophilic response lasts 3 days
Post-surgical
Neutrophil demargination
Epinephrine release/administration
Crying
Sepsis
Stress of delivery/labor; neutrophilic response lasts 3 days
Post-ictal
Erythrocyte transfusion
Diminished egress of neutrophils from the blood into the tissues
Adhesion molecule deficiency
Corticosteroid therapy
Spurious neutrophilia (platelet clumps read as neutrophils by automatic counters)